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=> d his 1

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, WPIDS, SCISEARCH, AGRICOLA'
     ENTERED AT 13:05:01 ON 22 DEC 2004)
L27          27 DUP REM L26 (13 DUPLICATES REMOVED)

=> d que 127
L1        72837 SEA LIU Y?/AU
L2          167 SEA L1 AND PARKINSON?
L3            3 SEA L2 AND KINASE?
L4            6 SEA L2 AND MIXED
L6          681 SEA MIXED(5A) LINEAGE(3A) KINASE?
L7           45 SEA L6 AND PARKINSON?
L8            1 SEA L7 AND ATP?
L9         3959 SEA PREVENT?(5A) NEURON?(5A) DEATH?
L10          10 SEA L6 AND L9
L13       53971 SEA NEURON?(5A) DEATH?
L14          82 SEA L13 AND L6
L15           1 SEA ATP? AND L14
L19          43 SEA NEURODEGENERAT? AND L6
L20           1 SEA L19 AND ATP?
L21           2 SEA ATP(5A) BIND? AND MIXED(5A) LINEAGE(3A) KINASE?
L22           4 SEA ATP(5A) BIND? AND MLK?
L23         120 SEA SEK? AND (PARKINSON? OR NEURODEGENERAT? OR NEURON?(5A)
                DEATH OR NEURON?(5A) APOPTO?)
L24           1 SEA L23 AND ATP?
L25          13 SEA L23 AND BIND?
L26          40 SEA L3 OR L4 OR L8 OR L10 OR L15 OR (L20 OR L21 OR L22) OR L24
                OR L25
L27          27 DUP REM L26 (13 DUPLICATES REMOVED)


=> d ibib abs 127 1-27

L27  ANSWER 1 OF 27  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:287758  HCAPLUS
DOCUMENT NUMBER:          140:302345
TITLE:                    Genes showing altered patterns of expression in the
                          central nervous system in multiple sclerosis and their
                          diagnostic and therapeutic use
INVENTOR(S):              Dangond, Fernando; Hwang, Daehee; Gullans, Steven R.
PATENT ASSIGNEE(S):       Brigham and Women's Hospital, Inc., USA
SOURCE:                   PCT Int. Appl., 139 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     WO 2004028339         A2    20040408    WO 2003-US29451          20030925
     WO 2004028339         A3    20040805
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR,
             TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2004156826         A1    20040812    US 2003-670766           20030925
PRIORITY APPLN. INFO.:                     US 2002-414219P      P    20020927
AB   The present invention identifies a number of gene markers whose expression is
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altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression.

L27 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:964915 HCAPLUS
DOCUMENT NUMBER: 141:422907
TITLE: Protein-protein interactions identifying drug targets and compositions and methods for treating neurological disorders and diseases
INVENTOR(S): Roch, Jean-Marc; Bartel, Paul; Heichman, Karen
PATENT ASSIGNEE(S): Myriad Genetics, Incorporated, USA
SOURCE: U.S. Pat. Appl. Publ., 247 pp., Cont.-in-part of U.S. Ser. No. 194,967.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004226056	A1	20041111	US 2004-776013	20040209
US 2002040484	A1	20020404	US 2001-948904	20010910
US 2002120947	A1	20020829	US 2001-949143	20010910
US 2002045201	A1	20020418	US 2001-970898	20011005
US 2002048769	A1	20020425	US 2001-970814	20011005
US 2002059653	A1	20020516	US 2001-970666	20011005
US 2002054876	A1	20020509	US 2001-971675	20011009
US 2002069424	A1	20020606	US 2001-971677	20011009
US 2002106676	A1	20020808	US 2001-973963	20011011
US 6653102	B2	20031125		
US 2002115606	A1	20020822	US 2001-973964	20011011
US 2002124273	A1	20020905	US 2001-973965	20011011
US 2002164655	A1	20021107	US 2001-973941	20011011
US 2002115607	A1	20020822	US 2001-975072	20011012
WO 2002032286	A2	20020425	WO 2001-US32186	20011016
WO 2002032286	A3	20030116		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 1998-113534P	P	19981222
US 1999-124120P	P	19990312
US 1999-141243P	P	19990630
US 1999-466139	B3	19991221
US 2000-240790P	P	20001017
US 2001-304775P	P	20010713
US 2001-948904	B2	20010910
US 2001-975072	B2	20011012
US 2002-194967	A2	20020715

AB The present invention generally relates to methods and compns. for treating neurol. disorders and diseases. The invention is based on the discovery of novel interactions involving several newly discovered interacting proteins in neurodegenerative disorders and neurodegenerative disease pathways, suggesting that modulation of such interactors may lead to alleviation of symptoms, delay of onset of symptoms, or treatment of the diseases or symptoms of the diseases. The interacting proteins identified in yeast two-hybrid assay systems include: focal adhesion

kinase 2 (FAK2), δ-catenin, glypican 1, HLA-B-associated transcript 3 (BAT3), low-d. lipoprotein receptor-related protein 2 (LRP2), transthyretin, protein PN7740, amyloid β (A4) precursor protein-binding family A member 1 (APBA1 or Mint1), presenilin 1 alternative transcript (PSI(467)), glutamate ammonia ligase, and others. In addition, the protein-protein interactions can facilitate the formation of protein complexes both in vitro and in vivo. This enables novel approaches for drug screening to select not only drug candidates that modulate the well-known drug targets employed in the interaction discovery process, but also drug candidates that modulate either the newly discovered interactor proteins or the protein-protein interactions themselves.

L27 ANSWER 3 OF 27 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:57124 SCISEARCH
THE GENUINE ARTICLE: 759DJ
TITLE: NADPH oxidase mediates lipopolysaccharide-induced neurotoxicity and proinflammatory gene expression in activated microglia
AUTHOR: Qin L Y (Reprint); **Liu Y X**; Wang T G; Wei S J; Block M L; Wilson B; Liu B; Hong J S
CORPORATE SOURCE: NIEHS, Neuropharmacol Sect, Lab Pharmacol & Chem, MD F1-01, POB 12233, Res Triangle Pk, NC 27709 USA (Reprint); NIEHS, Neuropharmacol Sect, Lab Pharmacol & Chem, Res Triangle Pk, NC 27709 USA; NIEHS, Natl Ctr Toxicogenom, Res Triangle Pk, NC 27709 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (9 JAN 2004) Vol. 279, No. 2, pp. 1415-1421.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Parkinson**'s disease is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra. We have previously reported that lipopolysaccharide (LPS)-induced degeneration of dopaminergic neurons is mediated by the release of proinflammatory factors from activated microglia. Here, we report the pivotal role of NADPH oxidase in inflammation-mediated neurotoxicity, where the LPS-induced loss of nigral dopaminergic neurons in vivo was significantly less pronounced in NADPH oxidase-deficient (PHOX-/-) mice when compared with control (PHOX+/+) mice. Dopaminergic neurons in primary mensencephalic neuron-glia cultures from PHOX+/+ mice were significantly more sensitive to LPS-induced neurotoxicity in vitro when compared with PHOX-/- mice. Further, PHOX+/+ neuron-glia cultures chemically depleted of microglia failed to show dopaminergic neurotoxicity with the addition of LPS. Neuron-enriched cultures from both PHOX+/+ mice and PHOX-/- mice also failed to show any direct LPS- induced dopaminergic neurotoxicity. However, the addition of PHOX+/+ microglia to neuron-enriched cultures from either strain resulted in reinstatement of LPS- induced dopaminergic neurotoxicity, supporting the role of microglia as the primary source of NADPH oxidase-generated insult and neurotoxicity. Immunostaining for F4/80 in mensencephalic neuron-glia cultures revealed that PHOX-/- microglia failed to show activated morphology at 10 h, suggesting an important role of reactive oxygen species (ROS) generated from NADPH oxidase in the early activation of microglia. LPS also failed to elicit extracellular superoxide and produced low levels of intracellular ROS in microglia-enriched cultures from PHOX-/- mice. Gene expression and release of tumor necrosis factor alpha was much lower in PHOX-/- mice than in control PHOX-/- mice. Together, these results demonstrate the dual neurotoxic functions of microglial NADPH oxidase: 1) the production of extracellular ROS that is toxic to dopamine neurons and 2) the amplification of proinflammatory gene

expression and associated neurotoxicity.

L27 ANSWER 4 OF 27 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004471064 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15380379
TITLE: In vivo activation of c-Jun N-terminal kinase signaling cascade prior to granule cell death induced by trimethyltin in the dentate gyrus of mice.
AUTHOR: Ogita Kiyokazu; Nitta Yuhki; Watanabe Mami; Nakatani Yuhki; Nishiyama Norito; Sugiyama Chie; Yoneda Yukio
CORPORATE SOURCE: Department of Pharmacology, Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan.. ogita@pharm.setsunan.ac.jp
SOURCE: Neuropharmacology, (2004 Sep) 47 (4) 619-30. Journal code: 0236217. ISSN: 0028-3908.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040922
Last Updated on STN: 20041219

AB The systemic administration of trimethyltin (TMT, 2.8 mg/kg, i.p.) induced granule cell death in the mouse dentate gyrus selectively 2 days later. The administration of TMT not only enhanced activator protein-1 DNA **binding**, along with an increase in expression of c-Jun and Fra-2, in the hippocampus 1 day later, but also facilitated phosphorylation of c-Jun N-terminal kinase (JNK) within the cytosol and nucleus. There was also a concomitant increase in the level of phosphorylated JNK kinase (MKK4/**SEK1**) in the cytosol 16-24 h after the administration. Moreover, TMT markedly elevated endogenous levels of both phosphorylated c-Jun and phosphorylated activating transcription factor-2 (ATF-2), in addition to activating JNK activity in the nuclear extracts obtained 16-24 h post-administration. Immunohistochemical analysis revealed that whereas Fra-2 and phosphorylated ATF-2 were expressed in the CA1 pyramidal cell layer predominantly, phosphorylated c-Jun was observed in both the CA1 pyramidal and dentate granule cell layers after TMT administration. Taken together, our data indicate that TMT activates the JNK pathway in the hippocampus prior to **neuronal** cell **death**. The prior activation of this pathway could be at least in part involved in the TMT-induced neural damage seen in the dentate granule cells of mice.

L27 ANSWER 5 OF 27 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:330132 SCISEARCH
THE GENUINE ARTICLE: 806PT
TITLE: Targeting the JNK MAPK cascade for inhibition: basic science and therapeutic potential
AUTHOR: Bogoyevitch M A (Reprint); Boehm I; Oakley A; Ketteman A J; Barr R K
CORPORATE SOURCE: Univ Western Australia, Sch Biomed & Chem Sci, Cell Signalling Lab, Nedlands, WA 6009, Australia (Reprint); Western Australian Inst Med Res WAIMR, Perth, WA, Australia; Univ Western Australia, Crystallog Ctr, Nedlands, WA 6907, Australia; Mahidol Univ, Inst Mol Biol & Genet, Nakhon Pathom 73170, Thailand
COUNTRY OF AUTHOR: Australia; Thailand
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEINS AND PROTEOMICS, (11 MAR 2004) Vol. 1697, No. 1-2, Sp. iss. SI, pp. 89-101. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 1570-9639.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 101
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The c-Jun N-terminal protein kinases (JNKs) form one subfamily of the mitogen-activated protein kinase (MAPK) group of serine/ threonine protein kinases. The JNKs were first identified by their activation in response to a variety of extracellular stresses and their ability to phosphorylate the N-terminal transactivation domain of the transcription factor c-Jun. One approach to study the function of the JNKs has included in vivo gene knockouts of each of the three JNK genes. Whilst loss of either JNK1 or JNK2 alone appears to have no serious consequences, their combined knockout is embryonic lethal. In contrast, the loss of JNK3 is not embryonic lethal, but rather protects the adult brain from glutamate-induced excitotoxicity. This latter example has generated considerable enthusiasm with JNK3, considered an appropriate target for the treatment of diseases in which **neuronal death** should be **prevented** (e.g. stroke, Alzheimer's and **Parkinson**'s diseases). More recently, these gene knockout animals have been used to demonstrate that JNK could provide a suitable target for the protection against obesity and diabetes and that JNKs may act as tumour suppressors. Considerable effort is being directed to the development of chemical inhibitors of the activators of JNKs (e.g. CEP-1347, an inhibitor of the MLK family of JNK pathway activators) or of the JNKs themselves (e.g. SP600125, a direct inhibitor of JNK activity). These most commonly used inhibitors have demonstrated efficacy for use in vivo, with the successful intervention to decrease brain damage in animal models (CEP-1347) or to ameliorate some of the symptoms of arthritis in other animal models (SP600125). Alternative Peptide-based inhibitors of JNKs are now also in development. The possible identification of allosteric modifiers rather than direct **ATP** competitors could lead to inhibitors of unprecedented specificity and efficacy.

L27 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:737915 HCAPLUS
DOCUMENT NUMBER: 139:256359
TITLE: Human cDNA sequences and their encoded proteins and diagnostic and therapeutic uses
INVENTOR(S): Zerhusen, Bryan D.; Patturajan, Meera; Kekuda, Ramesh; Miller, Charles E.; Rieger, Daniel K.; Pena, Carol E. A.; Shimkets, Richard A.; Li, Li; Berghs, Constance; Zhong, Mei; Casman, Stacie J.; Voss, Edward Z.; Boldog, Ferenc L.; Padigaru, Muralidhara; Smithson, Glennda; Shenoy, Suresh G.; Ji, Weizhen; Gorman, Linda; Vernet, Corine A. M.; Leite, Mario W.; Guo, Xiaojia; Anderson, David W.; Spytek, Kimberly A.; Gerlach, Valerie L.; Burgess, Catherine E.; Khramtsov, Nikolai V.; Ort, Tatiana; Ellerman, Karen; Rastelli, Luca; Agee, Michele L.; Chaudhuri, Amitabha; Chant, John S.; Dipippo, Vincent A.; Edinger, Shlomit; Eisen, Andrew; Gangolli, Esha A.; Giot, Loic; Ooi, Chean Eng; Rothenberg, Mark E.; Spaderna, Steven K.; Hjalt, Tord; Liu, Xiaohong; Taupier, Raymond J., Jr.; Catterton, Elina
PATENT ASSIGNEE(S): Curagen Corporation, USA
SOURCE: PCT Int. Appl., 562 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 145
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003076642	A2	20030918	WO 2002-US24459	20020802
WO 2003076642	A3	20041014		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003224982	A1	20031204	US 2002-187975		20020702
US 2004014053	A1	20040122	US 2002-210130		20020801
PRIORITY APPLN. INFO.:			US 2001-309501P	P	20010802
			US 2001-310291P	P	20010803
			US 2001-310951P	P	20010808
			US 2001-311292P	P	20010809
			US 2001-311979P	P	20010813
			US 2001-312203P	P	20010814
			US 2001-313156P	P	20010817
			US 2001-313201P	P	20010817
			US 2001-313702P	P	20010820
			US 2001-314031P	P	20010821
			US 2001-314466P	P	20010823
			US 2001-315403P	P	20010828
			US 2001-315853P	P	20010829
			US 2001-316508P	P	20010831
			US 2001-323936P	P	20010921
			US 2001-338078P	P	20011203
			US 2002-354655P	P	20020205
			US 2002-361764P	P	20020305
			US 2002-373825P	P	20020419
			US 2002-380971P	P	20020515
			US 2002-380980P	P	20020515
			US 2002-381039P	P	20020516
			US 2002-383761P	P	20020528
			US 2002-383887P	P	20020529
			US 2002-210130	A2	20020801
			US 2001-303046P	P	20010705
			US 2001-303828P	P	20010709
			US 2001-304502P	P	20010711
			US 2001-305011P	P	20010712
			US 2001-305262P	P	20010713
			US 2001-305673P	P	20010716
			US 2001-306085P	P	20010717
			US 2001-307536P	P	20010724
			US 2001-308228P	P	20010727
			US 2001-308877P	P	20010730
			US 2001-313643P	P	20010820
			US 2001-322640P	P	20010917
			US 2001-322716P	P	20010917
			US 2001-323484P	P	20010919
			US 2001-323821P	P	20010921
			US 2001-323948P	P	20010921
			US 2001-324711P	P	20010925
			US 2001-327893P	P	20011009
			US 2001-331768P	P	20011121
			US 2002-359191P	P	20020221
			US 2002-358939P	P	20020222
			US 2002-360923P	P	20020228
			US 2002-360830P	P	20020301
			US 2002-361178P	P	20020301
			US 2002-361748P	P	20020305
			US 2002-363429P	P	20020312
			US 2002-363683P	P	20020312
			US 2002-372141P	P	20020412
			US 2002-372967P	P	20020416
			US 2002-373051P	P	20020416
			US 2002-373063P	P	20020416
			US 2002-373280P	P	20020417

US 2002-373287P P 20020417
US 2002-373881P P 20020419

AB Disclosed herein are 49 cDNA sequences that encode novel human polypeptides that are members of various protein families. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivs., variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

L27 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:532691 HCAPLUS
DOCUMENT NUMBER: 139:95435
TITLE: Modified receptors on cell membranes for the discovery of therapeutic ligands
INVENTOR(S): Schwartz, Thue W.; Martini, Lene; Heydorn, Arne; Jorgensen, Rasmus
PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055914	A2	20030710	WO 2002-DK900	20021220
WO 2003055914	A3	20031023		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
DK 2001-1944 A 20011221
DK 2002-113 A 20020122
DK 2002-1043 A 20020703
US 2002-394122P P 20020703

AB A drug discovery method is provided for selecting a compound selected from the group consisting of a small organic substance, a biopharmaceutical, or an antibody or part thereof. The method comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compound or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors comprises capturing one or more receptors on the exterior cell surface in a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a method comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris.

Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L27 ANSWER 8 OF 27 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003280930 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12684520
TITLE: JNK-independent activation of c-Jun during neuronal apoptosis induced by multiple DNA-damaging agents.
AUTHOR: Besirli Cagri Giray; Johnson Eugene Malcolm Jr
CORPORATE SOURCE: Department of Neurology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: R01NS38651 (NINDS)
R37AG-12947 (NIA)
SOURCE: Journal of biological chemistry, (2003 Jun 20) 278 (25) 22357-66.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030617
Last Updated on STN: 20030822
Entered Medline: 20030821

AB Activation of the JNK pathway and induction of the AP-1 transcription factor c-Jun are critical for neuronal apoptosis caused by a variety of insults. Ara-C-induced DNA damage caused rapid sympathetic neuronal death that was associated with an increase of c-jun expression. In addition, c-Jun was phosphorylated in its N-terminal transactivation domain, which is important for c-Jun-mediated gene transcription. Blocking c-Jun activation by JNK pathway inhibition **prevented neuronal death** after stress. In contrast, neither the JNK inhibitor SP600125 nor the **mixed lineage kinase** inhibitor CEP-1347 **prevented** cytosine arabinoside-induced **neuronal death**, demonstrating that the JNK pathway was not necessary for DNA damage-induced neuronal apoptosis. Surprisingly, SP600125 or CEP-1347 could not block c-Jun induction or phosphorylation after DNA damage. Pharmacological inhibitors of cyclin-dependent kinase (CDK) activity completely prevented c-Jun phosphorylation after DNA damage. These results demonstrate that c-Jun activation during DNA damage-induced neuronal apoptosis was independent of the classical JNK pathway and was mediated by a novel c-Jun kinase. Based on pharmacological criteria, DNA damage-induced neuronal c-Jun kinase may be a member of the CDK family or be activated by a CDK-like kinase. Activation of this novel kinase and subsequent phosphorylation of c-Jun may be important in neuronal death after DNA damage.

L27 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:346477 HCAPLUS
DOCUMENT NUMBER: 139:83149
TITLE: Polyglutamine Expansion Induces a Protein-damaging

Stress Connecting Heat Shock Protein 70 to the JNK Pathway
AUTHOR(S): Merienne, Karine; Helmlinger, Dominique; Perkin, Gordon R.; Devys, Didier; Trottier, Yvon
CORPORATE SOURCE: INSERM, CNRS, Institut de Genetique et de Biologie Moleculaire et Cellulaire, Universite Louis Pasteur, Illkirch C.U. de Strasbourg, 67404, Fr.
SOURCE: Journal of Biological Chemistry (2003), 278(19), 16957-16967
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polyglutamine diseases, including Huntington's disease, designate a group of nine **neurodegenerative** disorders characterized by the presence of a toxic polyglutamine expansion in specific target proteins. Using cell and mouse models, the authors have shown that expanded polyglutamine led to activation of the stress kinase JNK and the transcription factor AP-1, which are implicated in **neuronal death**. Polyglutamine expansion-induced stress shared common features with protein-damaging stress such as heat shock, because activation of JNK involved inhibition of JNK phosphatase activities. Indeed, expanded polyglutamine impaired the solubility of the dual-specificity JNK phosphatase M3/6. Aggregation of M3/6 by polyglutamine expansion appeared to be indirect, because M3/6 was not recruited into polyglutamine inclusions. The heat shock protein HSP70, which is known to inhibit JNK during the heat shock response, suppressed polyglutamine-mediated aggregation of M3/6 and activation of JNK. Interestingly, levels of HSP70 were down-regulated by polyglutamine expansion. The authors suggest that reduction of HSP70 by expanded polyglutamine is implicated in aggregation and inhibition of M3/6 and in activation of JNK and AP-1.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:300182 HCAPLUS
DOCUMENT NUMBER: 139:98637
TITLE: Glycogen Synthase Kinase 3β Is a Natural Activator of Mitogen-activated Protein Kinase/Extracellular Signal-regulated Kinase Kinase Kinase 1 (MEKK1)
AUTHOR(S): Kim, Jin Woo; Lee, Ji Eun; Kim, Myung Jin; Cho, Eun-Gyung; Cho, Ssang-Goo; Choi, Eui-Ju
CORPORATE SOURCE: Graduate School of Life Science and Biotechnology, National Creative Research Initiative Center for Cell Death, Korea University, Seoul, 136-701, S. Korea
SOURCE: Journal of Biological Chemistry (2003), 278(16), 13995-14001
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glycogen synthase kinase 3β (GSK3β) is implicated in many biol. events, including embryonic development, cell differentiation, apoptosis, and insulin response. GSK3β has now been shown to induce activation of the mitogen-activated protein kinase kinase kinase MEKK1 and thereby to promote signaling by the stress-activated protein kinase pathway. GSK3β- **binding** protein blocked the activation of MEKK1 by GSK3β in human embryonic kidney 293 (HEK293) cells. Furthermore, co-immunopptn. anal. revealed a phys. association between endogenous GSK3β and MEKK1 in HEK293 cells. Overexpression of axin1, a GSK3β-regulated scaffolding protein, did not affect the phys. interaction between GSK3β and MEKK1 in transfected HEK293 cells. Exposure of cells to insulin inhibited the activation of MEKK1 by

GSK3β, and this inhibitory effect of insulin was abolished by the phosphatidylinositol 3-kinase inhibitor wortmannin. Furthermore, MEKK1 activity under either basal or UV- or tumor necrosis factor α-stimulated conditions was reduced in embryonic fibroblasts derived from GSK3β knockout mice compared with that in such cells from wild-type mice. Ectopic expression of GSK3β increased both basal and tumor necrosis factor α-stimulated activities of MEKK1 in GSK3β-/- cells. Together, these observations suggest that GSK3β functions as a natural activator of MEKK1.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 11 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003092602 EMBASE

TITLE: Pyrrolidine dithiocarbamate-induced **neuronal** cell **death** is mediated by Akt, casein kinase 2, c-Jun N-terminal kinase, and IκB kinase in embryonic hippocampal progenitor cells.

AUTHOR: Min Y.K.; Park J.H.; Chong S.A.; Kim Y.S.; Ahn Y.S.; Seo J.T.; Bae Y.S.; Chung K.C.

CORPORATE SOURCE: Dr. K.C. Chung, Department of Biology, College of Sciences, Yonsei University, Shinchon-dong 134, Seodaemun-gu, Seoul 120-749, Korea, Republic of. kchung@yonsei.ac.kr

SOURCE: Journal of Neuroscience Research, (1 Mar 2003) 71/5 (689-700).
Refs: 51
ISSN: 0360-4012 CODEN: JNREDK

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Pyrrolidine dithiocarbamate (PDTC) is known to induce cell death by the stimulation of intracellular zinc transport and subsequent modulation of nuclear factor-κB (NF-κB) activity. Zinc is a signaling messenger that is released by neuronal activity at many central excitatory synapses. Excessive synaptic release of zinc followed by entry into vulnerable **neurons** contributes to severe **neuronal** cell **death**. In the present study, we explored how PDTC modulates intracellular signal transduction pathways, leading to **neuronal** cell **death**. The exposure of immortalized embryonic hippocampal cells (H19-7) to PDTC within the range of 1-100 μM caused cell death in a dose-dependent manner. During the cell death, NF-κB activity increased in response to PDTC, and this activity corresponded well with the increase of intracellular free zinc levels, implying that the activation of NF-κB transmits the cell death signals of PDTC. Furthermore, PDTC caused the activation of IκB kinase (IKK), casein kinase 2 (CK2), phosphatidylinositol 3-kinase (PI-3K), and Akt, as well as mitogen-activated protein kinases (MAPKs), such as extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), but not p38 kinase. The blockade of PI-3K, JNK, and CK2 pathways resulted in a remarkable suppression of PDTC-induced cell death and also the activation of IKK, which subsequently led to a decrease of IκB phosphorylation. Although the overexpression of dominant-negative **SEK** in a transient manner did not inhibit the activation of Akt by PDTC, the transfection of kinase-inactive Akt mutants did cause a remarkable blockade of JNK activation, implying that Akt is present upstream of JNK in the PDTC-signaling pathways. Moreover, whereas selective CK2 inhibitors suppressed PDTC-induced JNK activation, the inhibition of JNK did not affect CK2 activity, suggesting that CK2 is directly related to the regulation of cell viability by PDTC and that the CK2-JNK pathway could be a downstream target of PDTC. Taken together, our results suggest that PDTC-mediated accumulation of intracellular zinc ions may affect cell viability by modulating several intracellular signaling pathways in

neuronal hippocampal progenitor cells. .COPYRGT. 2002 Wiley-Liss, Inc.

L27 ANSWER 12 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:136082 BIOSIS
DOCUMENT NUMBER: PREV200400137739
TITLE: Regulation of c-Jun N-terminal **kinase** activation in hydrogen peroxide induced neurotoxicity.
AUTHOR(S): Wang, Wei; Hou, Xiao-Yu; Gao, Can; **Liu, Yong**; Zong, Yan-Yan; Zhang, Guang-Yi [Reprint Author]
CORPORATE SOURCE: Research Center for Biochemistry and Molecular Biology, Xuzhou Medical College, 84 West Huaihai Road, Xuzhou, Jinagsu, 221002, China
wwang@ion.ac.cn; gyzhang@xzmc.edu.cn
SOURCE: Journal of Neurocytology, (February 2003) Vol. 32, No. 2, pp. 143-151. print.
ISSN: 0300-4864 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004
AB C-Jun N-terminal **kinase** 1 and 2 (JNK1/2) have been shown to be transiently activated and involved in neurotoxicity. We searched for possible upstream molecules, which are responsible for the regulation of hydrogen peroxide-(H2O2) induced JNK1/2 activation and JNK1/2-mediated apoptotic-like cell death in cultured rat cortical neurons. The results showed that JNK1/2 activation (monitored by anti-diphosphorylated JNK1/2 antibody) was largely prevented by elimination of extracellular Ca2+ or blockage of NMDA-receptors (NMDA-R), and was weakly but significantly decreased by blockage of L-type voltage-gated calcium channel (L-VGCC); furthermore, JNK1/2 activation was largely prevented by inhibition of Ca2+/calmodulin-dependent protein **kinase**-II (CaMKII) and protein-tyrosine **kinases** (PTK). We also found that H2O2-induced apoptotic-like cell death was partially prevented by elimination of extracellular Ca2+, or by inhibition of NMDA-R, L-VGCC, PTK and CaMKII, respectively. The above results suggest that in H2O2-induced neurotoxicity, JNK1/2 activation is mainly mediated by NMDA-R and L-VGCC. Consequently, PTK and CaMKII are critical intermediaries in JNK1/2 activation and are mainly responsible for JNK1/2-mediated apoptotic-like cell death.

L27 ANSWER 13 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003068009 EMBASE
TITLE: Dopaminergic modulation of neuronal activity in the striatum.
AUTHOR: **Liu Y.**; Hu G.
CORPORATE SOURCE: Y. Liu, Dept. of Pharmacology, Nanjing Medical University, Nanjing 210029, China. ghu@njmu.edu.cn
SOURCE: Chinese Pharmacological Bulletin, (2003) 19/1 (5-8).
Refs: 18
ISSN: 1001-1978 CODEN: ZYTOE8
COUNTRY: China
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Chinese
SUMMARY LANGUAGE: English; Chinese
AB The striatum is involved in diverse behaviors which depend on intact dopaminergic innervation. Recent electrophysiological studies have revealed that dopamine alters both voltage-dependent conductances and synaptic transmission, resulting in state-dependent modulation of target cells. This review makes clear predictions about how dopamine should alter the responsiveness of striatal neurons to extrinsic excitatory synaptic

activity.

L27 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:539792 HCAPLUS
DOCUMENT NUMBER: 137:104741
TITLE: Gene sequences from Methylococcus capsulatus as probes in DNA arrays for the determination of differential gene expression
INVENTOR(S): Birkeland, Nils Kare; Eidhammer, Ingvar; Jonassen, Inge; Jensen, Harald B.; Lien, Torleiv; Lillehaug, Johan R.; Lossius, Ivar; Eisen, Jonathan A.; Fraser, Claire M.; Durkin, A. Scott; Salzberg, Steven L.
PATENT ASSIGNEE(S): Unifob, Stiftelsen Universitetsforskning I Bergen, Norway; TIGR
SOURCE: PCT Int. Appl., 678 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055655	A2	20020718	WO 2002-NO19	20020114
WO 2002055655	A3	20021205		
WO 2002055655	C1	20030828		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: NO 2001-235 A 20010112
NO 2001-239 A 20010112

AB The invention related to method and systems for the determination of alteration of gene expression in Methylococcus capsulatus under a variety of conditions. A preferred embodiment of the invention relates to microarrays comprising polynucleotides or oligonucleotides representative for a selective number of the genes of M. capsulatus. Thus, whole genome random sequencing and assembly of M. capsulatus strain NCIMB 11132 was achieved with a total of 6- and 2-fold coverage of genome from BMC and BMD plasmid libraries. The genes are used as probes for the generation of an array system for the determination of differential expression due to alterations in incubation conditions, for example, at high or low concns. of Cu2+. Subsets of DNA sequences are identified for measurement of key metabolic features (metabolism of C and N, serine and butanediol pathways, lipid metabolism, and energy metabolism), regulator genes, and transport and secretion. The sequences for a total of 1840 DNA fragments and/or genes of M. capsulatus are provided.

L27 ANSWER 15 OF 27 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-187722 [24] WPIDS
CROSS REFERENCE: 2000-086442 [07]
DOC. NO. CPI: C2002-057884
TITLE: Method of screening a compounds ability to **prevent neuronal** cell **death** in mammals, affected with neurological conditions such as Huntington's disease, Alzheimer's disease.
DERWENT CLASS: B03 B04 D16 S03
INVENTOR(S): LIU, Y F
PATENT ASSIGNEE(S): (LIUY-I) LIU Y F
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002006606	A1	20020117	(200224)*		29

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002006606	A1 Provisional	US 1998-85439P	19980514
	Div ex	US 1998-156367	19980917
		US 2001-886964	20010621

PRIORITY APPLN. INFO: US 1998-85439P 19980514; US 1998-156367 19980917; US 2001-886964 20010621

AN 2002-187722 [24] WPIDS
CR 2000-086442 [07]
AB US2002006606 A UPAB: 20020610
NOVELTY - A compound found to have **Mixed-lineage kinase** (MLK) and/or c-Jun N-terminal kinase (JNK) inhibitor activity, is treated with mammalian neurons having activated MLK and/or JNK activity. A decrease in the number of dead neurons (in the presence of compound), in comparison to number of dead neurons(in the compounds absence), indicates the anti-neuronal apoptosis effect of the compound.

DETAILED DESCRIPTION - A compound is treated with MLK and/or JNK protein and a substrate. The level of JNK and/or MLK activity is measured, if the activity of the JNK and/or MLK is found to decrease in the presence of the compound (when compared to the activity in the absence of the compound), the compound is confirmed to be a JNK and/or MLK inhibitor. This compound is treated with mammalian neurons having activated **Mixed-lineage kinase** (MLK) and/or c-Jun N-terminal kinase (JNK) activity. The number of dead neurons is determined. A decrease in the number of dead neurons (in the presence of compound), in comparison to the normal number of dead neurons, indicates the ability of the compound to **prevent neuronal death**.

USE - For treating mammals with neurological diseases such as Huntington's disease or Alzheimer's disease, which involves nerve cell death by glutamate or kainic acid mediated excitotoxicity (claimed). Dwg.0/14

L27 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2002:404397 HCAPLUS
DOCUMENT NUMBER: 137:107579
TITLE: Signaling events in amyloid β-peptide-induced **neuronal death** and insulin-like growth factor I protection
AUTHOR(S): Wei, Wanli; Wang, Xiantao; Kusiak, John W.
CORPORATE SOURCE: Molecular Neurobiology Unit, Laboratory of Cellular and Molecular Biology, NIA, Intramural Research Program, National Institutes of Health, Baltimore, MD, 21224, USA
SOURCE: Journal of Biological Chemistry (2002), 277(20), 17649-17656
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amyloid β-peptide (Aβ) is implicated as the toxic agent in Alzheimer's disease and is the major component of brain amyloid plaques. In vitro, Aβ causes cell death, but the mol. mechanisms are unclear. The authors analyzed the early signaling mechanisms involved in Aβ toxicity using the SH-SY5Y neuroblastoma cell line. Aβ caused cell

death and induced a 2- to 3-fold activation of JNK. JNK activation and cell death were inhibited by overexpression of a dominant-neg. **SEK1** (**SEK1**-AL) construct. Butyrolactone I, a cdk5 inhibitor, had an addnl. protective effect against Aβ toxicity in these **SEK1**-AL-expressing cells suggesting that cdk5 and JNK activation independently contributed to this toxicity. Aβ also weakly activated ERK and Akt but had no effect on p38 kinase. Inhibitors of ERK and phosphoinositide 3-kinase (PI3K) pathways did not affect Aβ-induced cell death, suggesting that these pathways were not important in Aβ toxicity. Insulin-like growth factor I protected against Aβ toxicity by strongly activating ERK and Akt and blocking JNK activation in a PI3K-dependent manner. Pertussis toxin also blocked Aβ-induced cell death and JNK activation suggesting that Gi/o proteins were upstream activators of JNK. The results suggest that activation of the JNK pathway and cdk5 may be initial signaling cascades in Aβ-induced cell death.

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:214668 HCAPLUS
DOCUMENT NUMBER: 137:150359
TITLE: Identification of genes regulated by dexamethasone in multiple myeloma cells using oligonucleotide arrays
AUTHOR(S): Chauhan, Dharminder; Auclair, Daniel; Robinson, Elisabeth K.; Hideshima, Teru; Li, Guilan; Podar, Klaus; Gupta, Deepak; Richardson, Paul; Schlossman, Robert L.; Krett, Nancy; Chen, Lan Bo; Munshi, Nikhil C.; Anderson, Kenneth C.
CORPORATE SOURCE: The Jerome Lipper Multiple Myeloma Center, Department of Adult Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Oncogene (2002), 21(9), 1346-1358
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Our previous studies have characterized Dexamethasone (Dex)-induced apoptotic signaling pathways in multiple myeloma (MM) cells; however, related transcriptional events are not fully defined. In the present study, gene expression profiles of Dex-treated MM cells were determined using oligonucleotide arrays. Dex triggers early transient induction of many genes involved in cell defense/repair-machinery. This is followed by induction of genes known to mediate cell death and repression of growth/survival-related genes. The mol. and genetic alterations associated with Dex resistance in MM cells are also unknown. We compared the gene expression profiles of Dex-sensitive and Dex-resistant MM cells and identified a number of genes which may confer Dex-resistance. Finally, gene profiling of freshly isolated MM patient cells validates our in vitro MM cell line data, confirming an in vivo relevance of these studies. Collectively, these findings provide insights into the basic mechanisms of Dex activity against MM, as well as mechanisms of Dex-resistance in MM cells. These studies may therefore allow improved therapeutic uses of Dex, based upon targeting genes that regulate MM cell growth and survival.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 18 OF 27 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002619613 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12376704
TITLE: Subthalamic GAD gene therapy in a **Parkinson**'s disease rat model.
AUTHOR: Luo Jia; Kaplitt Michael G; Fitzsimons Helen L; Zuzga David S; **Liu Yuhong**; Oshinsky Michael L; During Matthew J
CORPORATE SOURCE: Functional Genomics and Translational Neuroscience

Laboratory, Department of Molecular Medicine and Pathology, University of Auckland, Auckland, New Zealand.
SOURCE: Science, (2002 Oct 11) 298 (5592) 425-9.
Journal code: 0404511. ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021012
Last Updated on STN: 20021214
Entered Medline: 20021127

AB The motor abnormalities of **Parkinson**'s disease (PD) are caused by alterations in basal ganglia network activity, including disinhibition of the subthalamic nucleus (STN), and excessive activity of the major output nuclei. Using adeno-associated viral vector-mediated somatic cell gene transfer, we expressed glutamic acid decarboxylase (GAD), the enzyme that catalyzes synthesis of the neurotransmitter GABA, in excitatory glutamatergic neurons of the STN in rats. The transduced neurons, when driven by electrical stimulation, produced **mixed** inhibitory responses associated with GABA release. This phenotypic shift resulted in strong neuroprotection of nigral dopamine neurons and rescue of the **parkinsonian** behavioral phenotype. This strategy suggests that there is plasticity between excitatory and inhibitory neurotransmission in the mammalian brain that could be exploited for therapeutic benefit.

L27 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2002:394536 HCAPLUS
DOCUMENT NUMBER: 137:304091
TITLE: **Mixed lineage kinase** family, potential targets for preventing neurodegeneration
AUTHOR(S): Maroney, Anna C.; Saporito, Michael S.; Hudkins, Robert L.
CORPORATE SOURCE: Cephalon Inc., West Chester, PA, 19380, USA
SOURCE: Current Medicinal Chemistry: Central Nervous System Agents (2002), 2(2), 143-155
CODEN: CMCCCO; ISSN: 1568-0150
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The c-Jun amino terminal kinase (JNK) cascade leading to c-Jun phosphorylation has been implicated in the neuronal cellular response to a variety of external stimuli including free radical oxidative stress, trophic withdrawal, amyloid toxicity and activation by death domain receptor ligands. Although the exact causes of neuronal loss in neurodegenerative diseases remain unknown, it has been hypothesized that response to these environmental stresses may be contributing factors. Agents which block the JNK signaling cascade have been proposed as a therapeutic approach for **preventing neuronal** cell **death** observed in a variety of neurodegenerative diseases including Parkinson's, Huntington's, and Alzheimer's disease. The JNKs are regulated through a sequential signaling cascade by a series of upstream **kinases** including the **mixed lineage kinases** (MLKs). Herein, we review the MLK family as a therapeutic target and provide evidence with CEP-1347, the most advanced MLK inhibitor currently in clin. trails for Parkinson's disease, that intervention at the MLK point in the JNK cascade may reduce the susceptibility of neurons to degenerate.

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 20 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:304518 BIOSIS
DOCUMENT NUMBER: PREV200300304518

TITLE: SUBTHALAMIC GLUTAMIC ACID DECARBOXYLASE GENE TRANSFER INDUCES HETEROTRANSMISSION AND NEUROPROTECTION in vivo.
AUTHOR(S): Luo, J. [Reprint Author]; Kaplitt, M. G.; Fitzsimons, H. L. [Reprint Author]; Zuzga, D. [Reprint Author]; **Liu, Y.** [Reprint Author]; Oshinsky, M. L. [Reprint Author]; During, M. J. [Reprint Author]
CORPORATE SOURCE: Neurosurgery, Thomas Jefferson Univ, Philadelphia, PA, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 461.2. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003

AB **Parkinsons** disease (PD) leads to an alteration in basal ganglia network activity, including disinhibition of the subthalamic nucleus (STN). This leads to excessive activity of the major output nuclei, the substantia nigra pars reticulata (SNr) and internal segment of the globus pallidus (GPi), which impact on motor activity and lead to the cardinal symptoms. Here we describe a genetic approach to test the hypothesis that the glutamatergic neurons of the STN can be induced to express glutamic acid decarboxylase (GAD) via rAAV-mediated gene transfer, and thereby change from an excitatory nucleus to a predominantly inhibitory system. Combined microdialysis and electrophysiology were used to assess the phenotypic shift induced by STN gene transfer. Our data show these excitatory glutamatergic neurons, when driven via electrical stimulation, result in **mixed** inhibitory responses associated with an increase in GABA release in the SN. This phenotypic shift also results in strong neuroprotection of nigral dopamine neurons in vivo associated with rescue of the **parkinsonian** behavioral phenotype. The combination of vesicular GABA transporter (VGAT) gene transfer with GAD did not confer any additional benefit. Further studies are focused on dissecting the mechanisms whereby GAD with or without VGAT co-expression mediates the phenotypic shift of excitatory neurons at physiological and ultrastructural levels. These data support a novel approach to the treatment of PD and the concept of plasticity between excitatory/inhibitory signaling and heterotransmission in the mammalian brain.

L27 ANSWER 21 OF 27 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:563155 SCISEARCH
THE GENUINE ARTICLE: 451KF
TITLE: CEP-1347 (KT7515), a semisynthetic inhibitor of the **mixed lineage kinase** family
AUTHOR: Maroney A C (Reprint); Finn J P; Connors T J; Durkin J T; Angeles T; Gessner G; Xu Z H; Meyer S L; Savage M J; Greene L A; Scott R W; Vaught J L
CORPORATE SOURCE: Cephalon Inc, 145 Brandywine Pkwy, W Chester, PA 19380 USA (Reprint); Cephalon Inc, W Chester, PA 19380 USA; Columbia Univ, Coll Phys & Surg, Dept Pathol, New York, NY 10032 USA; Columbia Univ, Coll Phys & Surg, Ctr Neurobiol & Behav, New York, NY 10032 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (6 JUL 2001) Vol. 276, No. 27, pp. 25302-25308.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 75

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CEP-1347 (KT7515) promotes neuronal survival at dosages that inhibit activation of the c-Jun amino-terminal kinases (JNKs) in primary embryonic cultures and differentiated PC12 cells after trophic withdrawal and in mice treated with 1-methyl-4-phenyl tetrahydropyridine. In an effort to identify molecular target(s) of CEP-1347 in the JNK cascade, JNK1 and known upstream regulators of JNK1 were co-expressed in Cos-7 cells to determine whether CEP-1347 could modulate JNK1 activation. CEP-1347 blocked JNK1 activation induced by members of the **mixed lineage kinase** (MLK) family (MLK3, MLK2, MLK1, dual leucine zipper kinase, and leucine zipper kinase), The response was selective because CEP-1347 did not inhibit JNK1 activation in cells induced by kinases independent of the MLK cascade. CEP-1347 inhibition of recombinant MLK members in vitro was competitive with **ATP**, resulting in IC,, values ranging from 23 to 51 nM, comparable to inhibitory potencies observed in intact cells. In addition, overexpression of MLK3 led to death in Chinese hamster ovary cells, and CEP-1347 blocked this death at doses comparable to those that inhibited MLK3 kinase activity. These results identify MLKs as targets of CEP-1347 in the JNK signaling cascade and demonstrate that CEP-1347 can block MLK-induced cell death.

L27 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:322906 HCAPLUS
DOCUMENT NUMBER: 135:59008
TITLE: Zn2+ induces stimulation of the c-Jun N-terminal kinase signaling pathway through phosphoinositide 3-kinase
AUTHOR(S): Eom, Soo-Jung; Kim, Eun Young; Lee, Ji Eun; Kang, Hyo Jung; Shim, Jaekyung; Kim, Seong Up; Gwag, Byoung Joo; Choi, Eui-Ju
CORPORATE SOURCE: National Creative Research Initiative Center for Cell Death, Graduate School of Biotechnology, Korea University, Seoul, S. Korea
SOURCE: Molecular Pharmacology (2001), 59(5), 981-986
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Zn2+, one of the most abundant trace metal ions in mammalian cells, modulates the functions of many regulatory proteins associated with a variety of cellular activities. In the central nervous system, Zn2+ is highly localized in the cerebral cortex and hippocampus. It has been proposed to play a role in normal brain function as well as in the pathophysiol. of certain **neurodegenerative** disorders. We here report that Zn2+-induced stimulation of the c-Jun N-terminal kinase (JNK) pathway in mouse primary cortical cells and in various cell lines. Exposure of cells to Zn2+ resulted in the stimulation of JNK and its upstream kinases including stress-activated protein kinase kinase and mitogen-activated protein kinase kinase kinase. Zn2+ also induced stimulation of phosphoinositide 3-kinase (PI3K). The Zn-induced JNK stimulation was blocked by LY294002, a PI3K inhibitor, or by a dominant-neg. mutant of PI3K. Furthermore, overexpression of Rac1N17, a dominant neg. mutant of Rac1, suppressed the Zn2+ - and PI3Kγ-induced JNK stimulation. The stimulatory effect of Zn2+ on both PI3K and JNK was repressed by the free-radical scavenging agent N-acetylcysteine. Taken together, our data suggest that Zn2+ induces stimulation of the JNK signaling pathway through PI3K-Rac1 signals and that the free-radical generation may be an important step in the Zn2+ induction of the JNK stimulation.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 23 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001281042 EMBASE

TITLE: Zn(2+)-induced ERK activation mediated by reactive oxygen species causes cell death in differentiated PC12 cells.
AUTHOR: Su Ryeon Seo; Seon Ah Chong; Lee S.-I.; Jee Young Sung; Ahn Y.S.; Chung K.C.; Jeong Taeg Seo
CORPORATE SOURCE: Dr. J.T. Seo, Department of Oral Biology, Yonsei Univ. College of Dentistry, Shinchon-dong 134, Seodaemun-gu, Seoul 120-752, Korea, Republic of. jeong@yumc.yonsei.ac.kr
SOURCE: Journal of Neurochemistry, (2001) 78/3 (600-610).
Refs: 54
ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recent studies have provided evidence that Zn(2+) plays a crucial role in ischemia- and seizure-induced **neuronal death**. However, the intracellular signaling pathways involved in Zn(2+)-induced cell death are largely unknown. In the present study, we investigated the roles of mitogen-activated protein kinases (MAPKs), such as c-Jun N-terminal kinase (JNK), p38 MAPK and extracellular signal-regulated kinase (ERK), and of reactive oxygen species (ROS) in Zn(2+)-induced cell death using differentiated PC12 cells. Intracellular accumulation of Zn(2+) induced by the combined application of pyrithione (5 μM), a Zn(2+) ionophore, and Zn(2+) (10 μM) caused cell death and activated JNK and ERK, but not p38 MAPK. Preventing JNK activation by the expression of dominant negative **SEK1** (**SEKAL**) did not attenuate Zn(2+)-induced cell death, whereas the inhibition of ERK with PD98059 and the expression of dominant negative Ras mutant (RasN17) significantly prevented cell death. Inhibition of protein kinase C (PKC) and phosphatidylinositol-3 kinase had little effect on Zn(2+)-induced ERK activation. Intracellular Zn(2+) accumulation resulted in the generation of ROS, and antioxidants prevented both the ERK activation and the cell death induced by Zn(2+). Therefore, we conclude that although Zn(2+) activates JNK and ERK, only ERK contributes to Zn(2+)-induced cell death, and that ERK activation is mediated by ROS via the Ras/Raf/MEK/ERK signaling pathway.

L27 ANSWER 24 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2002018598 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11432772
TITLE: Molecular mechanisms of the decision between life and death: regulation of apoptosis by apoptosis signal-regulating kinase 1.
AUTHOR: Matsuzawa A; Ichijo H
CORPORATE SOURCE: Laboratory of Cell Signaling, Graduate School, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8549, Japan.
SOURCE: Journal of biochemistry, (2001 Jul) 130 (1) 1-8. Ref: 65
Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011205
AB Coordination and balance between cell survival and apoptosis is crucial for normal development and homeostasis of multicellular organisms. Defects in control of this balance may contribute to a variety of diseases including cancer, autoimmune and **neurodegenerative** conditions. Although a large number of pro- and anti-apoptotic factors acting for or

against the final death event have been and are being discovered at an extraordinary pace with the recent progress in this area, the molecular mechanisms determining whether a cell lives or dies are not fully understood. Phosphorylation and dephosphorylation of intracellular effector molecules are the most common and important regulatory mechanisms in signal transduction and control a variety of cellular events from cell growth to apoptosis. Apoptosis signal-regulating kinase 1 (ASK1) is a member of the mitogen-activated protein (MAP) kinase kinase kinase family, which activates both the **SEK1**-JNK and MKK3/6-p38 MAP kinase pathways and constitutes a pivotal signaling pathway in cytokine- and stress-induced apoptosis. This review provides recent findings on the molecular mechanisms which determine cell fate such as survival, proliferation, differentiation or apoptosis, with special focus on the regulatory mechanisms of ASK1-mediated apoptosis.

L27 ANSWER 25 OF 27 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-086442 [07] WPIDS
CROSS REFERENCE: 2002-187722 [21]
DOC. NO. NON-CPI: N2000-067845
DOC. NO. CPI: C2000-024051
TITLE: Method of screening a compounds ability to **prevent neuronal** cell **death** in mammals, affected with neurological conditions such as Huntington's disease, Alzheimer's disease.
DERWENT CLASS: B03 B04 D16 S03
INVENTOR(S): LIU, Y F
PATENT ASSIGNEE(S): (LIUY-I) LIU Y F
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9958982	A1	19991118	(200007)*	EN	62
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
EP 1078268	A1	20010228	(200113)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 2002006606	A1	20020117	(200224)		29
JP 2002514767	W	20020521	(200236)		71
US 2002058245	A1	20020516	(200237)		
US 2003148395	A1	20030807	(200358)		
US 6811992	B1	20041102	(200472)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9958982	A1		WO 1999-US10416	19990512
EP 1078268	A1		EP 1999-922972	19990512
			WO 1999-US10416	19990512
US 2002006606	A1	Provisional	US 1998-85439P	19980514
		Div ex	US 1998-156367	19980917
			US 2001-886964	20010621
JP 2002514767	W		WO 1999-US10416	19990512
			JP 2000-548734	19990512
US 2002058245	A1	Provisional	US 1998-85439P	19980514
		Cont of	US 1998-156367	19980917
			US 2002-42614	20020109
US 2003148395	A1	Provisional	US 1998-85439P	19980514
		Cont of	US 1998-156367	19980917
			US 2003-360463	20030205
US 6811992	B1	Provisional	US 1998-85439P	19980514
			US 1998-156367	19980917

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1078268	A1 Based on	WO 9958982
JP 2002514767	W Based on	WO 9958982

PRIORITY APPLN. INFO: US 1998-156367 19980917; US
1998-85439P 19980514; US
2001-886964 20010621; US
2002-42614 20020109; US
2003-360463 20030205

AN 2000-086442 [07] WPIDS
CR 2002-187722 [21]
AB WO 9958982 A UPAB: 20020618
NOVELTY - A compound found to have **Mixed-lineage kinase** (MLK) and/or c-Jun N-terminal kinase (JNK) inhibitor activity, is treated with mammalian neurons having activated MLK and/or JNK activity. A decrease in the number of dead neurons (in the presence of compound), in comparison to number of dead neurons(in the compounds absence), indicates the anti-neuronal apoptosis effect of the compound.

DETAILED DESCRIPTION - A compound is treated with MLK and/or JNK protein and a substrate. The level of JNK and/or MLK activity is measured, if the activity of the JNK and/or MLK is found to decrease in the presence of the compound (when compared to the activity in the absence of the compound), the compound is confirmed to be a JNK and/or MLK inhibitor. This compound is treated with mammalian neurons having activated **Mixed-lineage kinase** (MLK) and/or c-Jun N-terminal kinase (JNK) activity. The number of dead neurons is determined. A decrease in the number of dead neurons (in the presence of compound), in comparison to the normal number of dead neurons, indicates the ability of the compound to **prevent neuronal death**.

USE - For treating mammals with neurological diseases such as Huntington's disease or Alzheimer's disease, which involves nerve cell death by glutamate or kainic acid mediated excitotoxicity (claimed).
Dwg.0/14

L27 ANSWER 26 OF 27 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-466665 [40] WPIDS
CROSS REFERENCE: 1996-188446 [19]
DOC. NO. CPI: C1998-141455
TITLE: Nucleic acid encoding Elf-1 protein that **binds** to EPH-type receptor - for production of Elf-1 protein, useful for regulating proliferation, differentiation, and survival of cells.
DERWENT CLASS: B04 D16
INVENTOR(S): CHENG, H; FLANAGAN, J G
PATENT ASSIGNEE(S): (HARD) HARVARD COLLEGE
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5795734	A	19980818	(199840)*		53

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5795734	A	CIP of	US 1994-308814	19940919
		CIP of	US 1995-393462	19950227
			US 1995-455001	19950531

PRIORITY APPLN. INFO: US 1995-455001 19950531; US
1994-308814 19940919; US
1995-393462 19950227

AN 1998-466665 [40] WPIDS
CR 1996-188446 [19]
AB US 5795734 A UPAB: 19981008
Nucleic aid (I) encodes a recombinant polypeptide (II) including an Elf-1 polypeptide (IIa) sequence at least 70% identical with 209 (2; murine) or 200 (4; chicken) amino acid (aa) sequences reproduced, or their fragments, which **binds** specifically to the EPH-type receptor (A).

Also claimed are:

(a) a recombinant transfection system comprising:

(i) gene construct including (I) plus eukaryotic control elements, and

(ii) gene delivery system;

(b) an expression vector containing (I) and replicable in eukaryotic and/or prokaryotic cells;

(c) host cells transformed with this vector;

(d) nucleic acid (Ia) encoding an Elf-1 polypeptide having a Cys4 motif at least 70% identical with the motif in (2) and/or (4) and **binding** specifically with mek4/**sek**-type (A), and

(e) chimaeric nucleic acid (Ib) encoding a fusion polypeptide (IIb) consisting of (IIa) and second unrelated aa sequence, able to **bind** specifically to (A).

USE - The cells of (c) are used to produce (II) which modulates proliferation, differentiation and/or survival of (A)-expressing cells by stimulating or antagonising intracellular signalling mediated by (A). Typical of many potential applications are increasing survival of neuronal cells in culture (e.g. where intended for transplantation), also therapeutically in increase neuron survival (e.g. treatment of Alzheimer's or **Parkinson**'s diseases), to prevent nervous system and lymphatic tumours, to induce differentiation of hepatocytes to form an artificial liver, to induce cartilage and bone formation.

(II) are also used to raise specific antibodies (Ab) and to screen for potential inhibitors/potentiators of receptor **binding**. Ab are useful as antagonists, as immunoassay reagents (for diagnosing neurological disease, neoplastic and hyperplastic diseases) and for screening expression libraries. (I), or its fragments, are useful in gene therapy, to detect transformed cells, to determine levels of Elf-1 nucleic acid, to identify mutations in the Elf-1 gene (to assess risk of disease), while its antisense sequences can be used therapeutically. (IIb) are useful as affinity probes to detect receptors.
Dwg.0/5

L27 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:626152 HCAPLUS
DOCUMENT NUMBER: 129:311931
TITLE: Activation of JNK pathway and induction of apoptosis by manganese in PC12 cells
AUTHOR(S): Hirata, Yoko; Adachi, Kayo; Kiuchi, Kazutoshi
CORPORATE SOURCE: Laboratory for Genes of Motor Systems, Bio-Mimetic Control Research Center, The Institute of Physical and Chemical Research (RIKEN), Nagoya, 463-0003, Japan
SOURCE: Journal of Neurochemistry (1998), 71(4), 1607-1615
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Manganese is known to induce neurol. disorders similar to **parkinsonisms**. A dopamine deficiency has been demonstrated in **Parkinson**'s disease and in chronic manganese poisoning, suggesting that the mechanisms underlying the neurotoxic effects of the metal ion are related to a functional abnormality of the extrapyramidal system. However, the details have yet to be elucidated. Here the authors report that manganese causes characteristic internucleosomal DNA fragmentation, a biochem. hallmark of apoptosis, in PC12 cells. It was transcription dependent, relatively specific for manganese, and blocked in Bcl-2-overexpressed PC12 cells. The results indicate that apoptosis may play a role in the dopaminergic neurotoxicity associated with manganese, the

first metal to be reported to induce this form of cell death. The early biochem. events show the impairment of energy metabolism, and the process may require new synthesis of proteins such as c-Fos and c-Jun. In addition, manganese induces phosphorylation of c-Jun at Ser63 and Ser73 and **SEK1**/MKK4 (c-Jun N-terminal kinase kinase) at Thr258 and tyrosine phosphorylation of several proteins. These results indicate that manganese activates specific signal cascades including the c-Jun N-terminal kinase pathway.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT